

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Sustained Release Pharmaceutical Compositions

We, LABORATOIRE DE RECHERCHES
PHYSIQUES S.à.r.l., a body Corporate organised
and existing under the laws of Switzerland,
of Villa Marguerite, Veyrier, Geneva, Switzer-
land, do hereby declare the invention, for
which we pray that a patent may be granted
to us, and the method by which it is to be
performed, to be particularly described in and
by the following statement:—

This invention relates to sustained release
pharmaceutical compositions.

According to this invention there is provided
a sustained-release pharmaceutical composi-
tion in the form of a coated pellet or tablet
containing a pharmaceutically active ingre-
dient soluble in the fluids of the gastrointes-
tinal tract, wherein the coating layer com-
prises one or more areas impermeable by said
fluids and by said pharmaceutically active ingre-
dient, and one or more other areas pro-
vided by a dialysing membrane permeable
by said fluids and by said ingredient and
through which said ingredient may diffuse
gradually when the tablet is administered. It
will be apparent that by varying the relative
sizes of the impermeable and permeable areas
in the coating layer tablets or pellets may be
produced having different rates of release.

The dialysing membrane used to form the
permeable areas of the coating may be formed
from a wide variety of natural and synthetic
film-forming materials. Desirably the film-
forming materials as well as ion exchange re-
having ion-exchange properties. Typical film
forming materials as well as ion exchange re-
sins to be used in conjunction therewith are
illustrated in U.S. Patent Specification No.
2846057. Suitable film forming materials in-
clude cellulose acetate, acrylic polymers,
phenolic polymers and collodion. Typical ion
exchange materials include sulfonated poly-
styrene, resorcinol-type resins, carboxylic acid
resins, phenolformaldehyde polyamine resins,

polystyrene polyamine resins and polystyrene
quaternary amine resins.

In the past it has been noted that in certain
cases the surface of sustained release pellets
and tablets become coated over a period of
time with an insoluble deposit of calcium,
thus reducing the rate of diffusion. This is
particularly so in tablets or pellets admini-
stered to ruminant animals where the pellet
may remain in the rumen for some consider-
able period of time. In order to prevent this
fall off in the rate of diffusion of the pharma-
ceutical ingredient, it is desirable to incor-
porate in the pellets or tablets provided in
accordance with the invention a non-toxic pH
buffering substance capable of maintaining
the pH at the surface of the tablet at or below
about 7.3. Suitable buffering substances in-
clude sodium salicylate, sodium citrate and
other mildly acidic salts. The buffering sub-
stance may be incorporated in the pellet or
in the permeable areas of the coating.

In one form of the invention the tablet or
pellet as a whole may be enveloped in a
porous membrane, the outer surface of which
is coated in selected areas with a layer of im-
permeable and insoluble material. For example
the outer surface of the membrane could be
over-printed with a checkerboard pattern thus
reducing the total amount of diffusable sur-
face area available.

In another embodiment the pellet or tablet
may comprise a rigid non-diffusible plastics
jacket or shell enclosing the medicament in
a central hollow chamber but having a
number of passageways passing through the
shell sealed, for example, at their outer ends,
by the dialysing membrane. In a modifica-
tion of this arrangement the pellet or tablet
may comprise a non-toxic rigid non-diffusible
plastics body, e.g. of polymethylmethacrylate
or polytetrafluoroethylene, having a plurality
of passageways therein extending from the

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centre of the body outwardly to the surface, and which accommodate the pharmaceutical ingredient, the outer ends of the passageways being sealed by the dialysing membrane. These two arrangements are particularly advantageous because the rigid plastics shell or body has little or no moisture absorption and the tablets are therefore not so susceptible to swelling and rupture of the membrane areas.

In another arrangement, the pharmaceutically active ingredient in compressed dosage form is coated with the dialysing membrane. This is then encased in a rigid plastics jacket having a number of apertures therein so as to expose the underlying areas of the membrane.

The pharmaceutical ingredient of the tablets or pellets of this invention may be in liquid, crystalline or powder form. The invention is most applicable to drugs of which the dosage rate is only a few milligrams a day. With drugs requiring a higher dosage rate the physical size of the tablet or pellet presents administration difficulties. A typical pharmaceutical ingredient which may be incorporated in the tablets or pellets of this invention is oxytetracycline hydrochloride.

As a specific embodiment to illustrate this invention, oxytetracycline hydrochloride in powder form was compressed into a length of polytetrafluoroethylene tubing. The tube was then cut into short lengths suitable for oral administration and the ends of each length sealed with a dialysing membrane of cellulose acetate. The individual pellets thus formed were tested for release rate and this was found to be constant at 0.001 mg. per hour. Further no swelling or deformation was noted after a long term test lasting over a period of 10 days. In an alternative embodiment oxytetracycline hydrochloride powder was filled into hollow spherical pellets formed from a rigid plastics material having a single window or aperture in the shell 2 mm. in diameter. After filling the window was sealed with a porous membrane of cellulose acetate. Diffusion rates were obtained as follows.

Day	Period (hrs)	Rate (mg./hrs.)
1	1—4	0.22
	1—8	0.12
2	1—5	0.06
	1—8	0.09
3	1—7	0.07

It will be observed that after the first day, a uniform rate of drug diffusion was attained with respect to the oxytetracycline component of the mixture. As a matter of fact, rates as low as 0.04 mg./hr have even been achieved with oxytetracycline after 500—1,000 hours of testing, with the average values falling within the 0.05—0.07 mg./hr. range on a 1,000-hour basis.

In connection with the manufacture of the desired pellets of this invention, the required printing thereon, which is needed to modify

the total amount of diffusible surface, is achieved by the use of conventional means such as, for example, by the use of inking rollers (similar to imprinting a trademark on a pellet) or by dipping or spraying. The production of the pellet may be by means of extrusion, compression or any combination of these moulding techniques. For example, the active ingredient may be dipped or sprayed or mixed with a film-forming composition and compression moulded. It is the finally coated by passing the preformed pellet through an extrusion mould to receive the final coating. Needless to say, any standard tablet-forming process can easily be adapted to include the aforementioned coating step. Although no one specific pressure is ideally suitable for or even really absolutely necessary in the pellet production of this invention, since this has no real direct influence or effect on the release rate of the drug contained in said pellet, it is desirable to employ an appropriate pressure with powdered drugs which will not be so high as to exclude the availability of its content to the action of a solvent. In the instance of a liquid drug encapsulated in the controlled diffusion membrane, the rigid non-diffusing envelope with the selected orifice pattern may be formed by extrusion and the orifices sealed by means of a diffusion membrane. Liquid drugs prepared in this manner have included antibiotics, sedatives and vermifuges.

WHAT WE CLAIM IS:—

1. A sustained release pharmaceutical composition in the form of a coated pellet or tablet containing a pharmaceutically active ingredient soluble in the fluids of the gastrointestinal tract, wherein the coating layer comprises one or more areas impermeable by said fluids and by said pharmaceutically active ingredient and one or more other areas provided by a dialysing membrane permeable by said fluids and by said ingredient and through which said ingredient may diffuse gradually when the tablet is administered.
2. A composition as claimed in claim 1 wherein the pharmaceutically active ingredient is oxytetracycline hydrochloride.
3. A composition according to claim 1 or 2, wherein the dialysing membrane comprises an ion-exchange material capable of controlling the rate of release of the pharmaceutically active ingredient.
4. A composition as claimed in claim 3 wherein the ion-exchange material is a sulfonated polystyrene.
5. A composition as claimed in any one of claims 1—4, wherein the whole tablet or pellet is enveloped by the dialysing membrane and the impermeable areas are provided by coating the membrane with a layer of impermeable material extending over selected areas of the membrane.

6. A composition according to any one of claims 1—4, wherein the tablet or pellet is coated with a rigid plastics jacket encompassing the compressed dosage form, said jacket having one or more pasageways therethrough for passage of the medicament, said passageway or passageways being sealed by said dialysing membrane.
- 5 7. A composition as claimed in claim 6 which also contains a pH buffering substance compatible with the living animal system and capable of maintaining the pH at the surface of the tablet at or below about 7.3.
8. A composition as claimed in claim 6 wherein the plastics material is polymethyl methacrylate.
9. A composition as claimed in claim 6 wherein the plastics material is polytetrafluoroethylene.
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